

REMARKS

This response is prepared in substantially the same order as the issues appear in the Office Action dated March 09, 2004.

Claim Rejections - 35 USC §102 (b)

Claims 1, 2, 6-8, 10 and 11 are rejected over Sudo *et al.*, (WO 99/58662, 11/18/99; in English EP 1 088 888 A1, hereinafter Sudo).

For the following reasons, Applicants respectfully traverse the Examiner's basis for and conclusion of the rejections.

I. Legal Standard

The initial burden is on the Patent and Trademark Office to establish a *prima facie* case of anticipation. *See MPEP* §2112.

"Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration." *W. L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984), emphases added. *Accord, Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360, 47 USPQ2d 1516, 1522 (Fed. Cir. 1998); *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003). *See Also MPEP* §2131.

Further, "[a]nticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481, 485 (Fed. Cir. 1984) (citing *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983)), emphasis added. "The elements must be arranged as required by the claim, but this is not an ipsissimis verbis test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990)." Cited in *MPEP* §2131.

In addition, the prior art reference must be enabling. *See for example, Akzo N. V. v. U. S. Int'l Trade Commission*, 808 F.2d 1471, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986) (citing *In re Brown*, 329 F.2d 1006, 1011, 141 USPQ 245, 249 (CCPA 1964)). *Accord, Crown*

Operations International, Ltd. v. Solutia Inc., 289 F.3d 1367, 1375, 62 USPQ2d 1917, 1921 (Fed. Cir. 2002).

Inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. See *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citing *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991))

II. Analysis

Applicants discuss independent claims, Claims 1 and 10, first.

Assuming, but expressly without admitting, for 102 argument purposes only that the Examiner has cited all the individual elements of claims 1, Applicants respectfully submit that the Examiner has overlooked an important part of the disclosure of *Sudo*.

In *Sudo*, the inventors state that "[a] fusion protein containing ..., from its N-terminal to C-terminal direction: a)..." Abstract. In claim 1, essentially the same language appears. In Applicants' understanding, *Sudo* teaches a fusion protein of the following sequence:

Signal sequence–Fc–Peptide Linker–Target Protein

where the "Target Protein" can be erythropoietin (EPO). Further, the "FcEPO" portion is explicitly used in paragraph [0036] (*Sudo*, page 7, lines 2-10)

In contrast, Claim 1 of Applicants' invention is for "[a] recombinant HuEPO-L-vFc fusion protein comprising..." At a minimum, the elements, Fc, L and protein, are clearly "*not as arranged*" as those in *Sudo*, regardless whether they are the same in *Sudo* and Applicants' claimed invention. There is no unity between *Sudo* and Claim 1 of Applicants' invention. Therefore, *Sudo* cannot anticipate, *prima facie*, Claim 1 under both MPEP rules and the holdings of the Federal Circuit. Thus, the burden has not shifted to Applicants to show no anticipation.

Regarding Claim 10, the Examiner does not point to anywhere in *Sudo* that teaches or discloses expressly "... (b) growing the cell line under conditions the recombinant protein is expressed in its growth medium in excess of 10 µg per million cells in a 24 hour period; and (c) purifying the expressed protein from step (b), wherein the recombinant fusion protein exhibits an

enhanced in vitro biological activity of at least 2 fold relative to that of rHuEPO on a molar basis.” There is no unity, thus *Sudo* cannot anticipate, *prima facie*, Claim 10 of this application.

In addition, the Examiner does not allege anywhere in the Office Action (that Applicants can find) that *Sudo* anticipates the rejected Claims 1 and 10 inherently. Even if the Examiner did, Applicants respectfully submit that the Examiner has not pointed to anywhere in *Sudo*, the cited prior art, that any inherency of the missing element(s) or different arrangement exists necessarily. Because the lack of unity between *Sudo* and Claims 1 and 10 of this invention is so clear once the Examiner considers the overlooked aspect of *Sudo*, Applicants respectfully submit that they do not need to discuss whether *Sudo* is enabling at this time.

For the same reasoning and arguments regarding lack of unity, the Examiner has failed to show *prima facie* anticipation of Claims 2, 6-8 and 11 either. These claims depend from Claim 1 or Claim 10 respectively.

Finally, while Applicants respectfully submit that the burden has not shifted to them to prove no anticipation, they want to add another argument in support of their position. “[A]nticipation is the epitome of obviousness...” *Jones v. Hardy*, 727 F.2d 1524, 1529, 220 USPQ 1021, 1025 (Fed. Cir. 1984). Applicants observe that the Examiner has to rely on *Sudo in view of Sytkowski*, not *Sudo* in and by itself, to support the ground of the 103 obviousness rejection of Claims 1, 2 and 10 -- those claims rejected under both 102 and 103, *see* paragraphs in the Office Action under 103 rejections, pages 3 and 4. Since *Sudo* cannot support 103 (a) obviousness rejections on its own disclosures, *Sudo*, *by definition*, cannot anticipate the claimed inventions in the rejected Claims 1, 2, and 10. *Jones v. Hardy*, *supra*. Because Claims 6-8 and 11 depend from Claim 1 and Claim 10 respectively and contain additional and more restrictive and stringent limitations, they cannot be anticipated by *Sudo* either.

III. Conclusion regarding 102 rejections

For the foregoing reasons, Applicants respectfully submit that the Examiner has not met the initial burden of establishing a *prima facie* case of anticipation in the Office Action. *Sudo* does not anticipate the claimed inventions of Claims 1, 2, 6-8, 10, and 11 either explicitly or inherently. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections of Claims 1, 2, 6-8, 10, and 11.

Claim Rejections - 35 USC §103 (a)

Claims 1, 2, 10, 12, and 13 are rejected over *Sudo et al.*, (WO 99/58662, 11/18/99; in English EP 1 088 888 A1, hereinafter *Sudo*) in view of *Sytkowski et al.*, (Journal of Biological Chemistry 274:24773-24778, 1999, hereinafter *Sytkowski*).

For the following reasons and arguments, Applicants respectfully traverse the Examiner's basis for and conclusion of the obviousness rejections.

I. Legal Standard

"In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation, or teaching *in the prior art* that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention." *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 2001, *emphasis added*).

The Federal Circuit in *In re Vaeck*, 947 f.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) explains that the prior art reference (or references when combined) must teach or suggest all the claimed limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *See also MPEP* §2142.

In addition, a showing of obviousness requires a motivation or suggestion to combine or modify prior art references, coupled with a reasonable expectation of success. *see Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000), *accord, Boeringer v. Schering-Plough*, (Case 02-1026, -1027, decided February 21, 2003)

It is impermissible to use the claimed invention as an instruction manual, road map, or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. The Federal Circuit has stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (quoting *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)). The examiner "...cannot pick and choose among the individual elements of assorted prior art references to recreate the

claimed invention.” *SmithKline Diagnostics Inc. v. Helena Laboratories Corp.*, 8 U.S.P.Q. 2d 1468, 1475 (Fed. Cir. 1988).

Finally, the Federal Circuit Court recently reiterates that “[i]n making the assessment of differences, section 103 specifically requires consideration of the claimed invention “as a whole.” Inventions typically are new combinations of existing principles or features. *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983) (noting that “virtually all [inventions] are combinations of old elements.”). The “as a whole” instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result - often the very definition of invention.” *Ruiz v. A.B. Chance Company*, (Case No. 03-1333, decided January 29, 2004).

II. **Analysis**

Applicants first discuss independent claims, Claims 1 and 10.

As Applicants point above in the 102 anticipation **Analysis** section, *Sudo* teaches a fusion protein from its N-terminal to C-terminal direction “Signal sequence–Fc–Peptide Linker–Target Protein.” The Examiner correctly points out that *Sytkowski* teaches fusion proteins consisting of *two* human erythropoietin domains linked by a specific 17 amino acid flexible peptide linker. (Office Action page 4, first full paragraph, emphasis added by Applicants). However, the Examiner has not pointed to anywhere in *Sudo* or *Sytkowski* a fusion protein EPO-Linker-Fc.

In addition to the arguments below, Applicants also rely on, but will not repeat, the arguments they have already presented above in the 102 **Analysis** section.

Applicants respectfully submit that the Examiner has not shown that *Sytkowski* fills the gap. Indeed, by teaching a 17-amino acid flexible peptide linker between two EPO domains, *Sytkowski* cannot and does not fill the gap. Applicants respectfully submit that the Examiner has engaged in impermissible hindsight reconstruction of the claimed invention. The Examiner has not pointed to anywhere *in Sudo* teaching or suggesting, expressly or implicitly, fusion proteins

of HuEPO-L-HuEPO of *Sytkowski* or how *Sudo* may be applied to such a fusion protein. Similarly, the Examiner has failed to point out anywhere *in Sytkowski* teaching or suggesting, expressly or implicitly, that their techniques can be used for S-Fc-L-HuEPO fusion protein of *Sudo*, let alone HuEPO-L-vFc fusion protein of Applicants' claimed invention. As Applicants already point out, *Sudo* discloses from its N-terminal to C-terminal direction Signal sequence–Fc–Peptide Linker–Target Protein (S-Fc-L-HuEPO). Applicants do not see how the Examiner can reach the conclusion, without using Applicants' application as a roadmap, that “[t]he motivation and expected success is provided by Sytkowski *et al.* who demonstrate that the length of the peptide linker functions to aid in stability and inhibit steric hinderance.” Applicants respectfully request that the Examiner provide evidence that how one-skilled-in-the-art can be motivated to combine references teaching S-Fc-L-HuEPO and HuEPO-L-HuEPO to experiment and expect success for an invention of HuEPO-L-vFc without using Applicants' application as a template or roadmap or instruction manual.

Applicants certainly appreciate and recognize that the Examiner may have additional references and/or possess personal knowledge to which Applicants are not privy. If this is the case, Applicants respectfully request that the Examiner provide them with such references or an affidavit to apprise them of how the gap can be bridged. *MPEP* §707.

Applicants respectfully believe that the Examiner has not carried the initial burden of proving a *prima facie* case of obviousness and that the burden has not shifted to Applicants to prove nonobviousness of their claimed invention. However, they still provide the following additional but unnecessary observation regarding their claimed invention solely for the purposes of discussion and the Examiner's consideration.

Sudo makes the following statement in their disclosure, “[t]he inventors of the present invention *conducted various researches on the fusion techniques* in order to achieve the foregoing objects.” (page 3, lines 1-2 of the first paragraph [0008], emphasis added by Applicants) This statement clearly teaches away the invention of Claim 1 because, instead of motivating a person of ordinary skill in the art, *Sudo* tends to discourage others from experimenting with other possibilities, which presumably have already been investigated by the inventors of *Sudo*. Such teaching-away is strong evidence of nonobviousness of Applicants' claimed invention.

Regarding Claim 10, Applicants rely on the same reasoning and arguments above for Claim 1 because they remain sound and non-refutable even though Claim 10 does not specifically recite HuEPO-L-vFc. But there are additional limitations in this method claim. The Examiner does not point to anywhere in *Sudo* or *Sytkowski* that teaches or discloses or suggests expressly or implicitly “...(b) growing the cell line under conditions the recombinant protein is expressed in its growth medium in excess of 10 µg per million cells in a 24 hour period; and (c) purifying the expressed protein from step (b), wherein the recombinant fusion protein exhibits an enhanced in vitro biological activity of at least 2 fold relative to that of rHuEPO on a molar basis.” The gap remains unfilled and un-bridged.

Here again, other than a conclusory statement, the Examiner has not pointed to, as she must, anywhere in *either Sudo or Sytkowski* that there is motivation for one ordinarily skilled in the art to combine these two references or to experiment with the claimed invention of Claim 10, let alone a reasonable expectation of success from such experimentation. It is worth repeating again that *Sytkowski* teaches EPO-L-EPO and the Examiner has not pointed to any express or implicit teachings or suggestions of a fusion protein containing vFc or how a 17-amino acid flexible linker might change the properties. Furthermore, the last full paragraph in *Sytkowski* (page 24777, above *Acknowledgment*) explicitly points out the unpredictable nature of research even for HuEPO-L-HuEPO itself. It is hard for Applicants to see how the Examiner can conclude, without using Applicants’ invention as a template, that there can be reasonable expectations of success when the teachings of *Sytkowski* are combined with a distinctly different type of fusion protein of *Sudo*, which does not contain *two* HuEPO domains.

Both the Court of Appeals for the Federal Circuit and MPEP rules have repeatedly warned against finding motivation and reasonable expectation of success in Applicants’ own patent application. Such findings must be shown to exist in the cited prior art references, *i.e.* *Sudo* or *Sytkowski*, for the instant invention under examination. See *In re Vaeck* and MPEP §2142. View Claim 10 *as a whole*, as required by 35 USC §103, Applicants respectfully submit that their claimed invention cannot be and is not obvious over *Sudo* in view of *Sytkowski* to one skilled in the art.

Just like in the situation of Claim 1, Applicants appreciate and recognize that the Examiner may have additional references and/or personal knowledge to which Applicants are not

privity. If so, Applicants respectfully request that the Examiner provide them with such references or an affidavit to apprise them of how the gap can be bridged. *MPEP* §707.

Finally, Claims 2, 12 and 13 depend from Claims 1 and 10 respectively. For the same reasons stated above in this **Analysis** section, Claims 2, 12 and 13 should be allowable too because they contain additional and more restrictive and stringent limitations.

III. Conclusion regarding 103 rejections

Applicants respectfully submit that the Examiner has not carried the burden of proving Claims 1, 2, 10, 12, and 13 are *prima facie* obvious over *Sudo* in view of *Sytkowski*. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the 103(a) obviousness rejections.

Claim Rejections - 35 USC §112 Second Paragraph

Claims 7-10, and 20 are rejected under 35 USC §112 second paragraph over the term “CHO-derived cell line.”

Applicants appreciate that the Examiner takes time to suggest a new language for these claims – “CHO cell line transfected with DNA encoding the recombinant HuEPO-L-vFC fusion protein...” Claims 7-10 and 20 are amended in accordance with the Examiner’s suggestion. These amendments are support by the specification at least in paragraphs [0013], [0016], [0017], [0027] and [0028]. No new matter is added to or incorporated into the claims by the amendments.

Accordingly, the amendments should overcome the ground of the rejections.

Claims with Conflicting Status

Claims 3, 14 and 15 are “rejected” in the Office Action Summary, item 6), and by implication, “[n]o claims are allowed” (Conclusion Office Action, page 5) without explanation or basis.

In the Office Action the Examiner does not cite any grounds that Applicants can find to support rejections of Claims 3, 14 and 15. As such, Applicants assume that they are allowed. If not, Applicants respectfully request that the Examiner clarify this matter so that they can better respond to the issues. However, in view of the amendments, discussion and reasoning presented hereinabove, Applicants believe that these three claims are allowable in their current form.

Conclusion

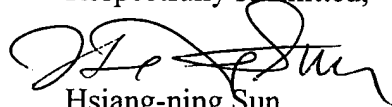
No new matter is introduced into the application by any and all of the amendments made herein to the claims. All the amendments to the claims are supported by the disclosure of the originally filed application. Applicants respectfully request that the Commissioner enter these Amendments into the application as submitted herein.

Applicants believe that they have discussed all the aspects of the issues raised in the Office Action and respectfully submit that the Examiner has not carried the burden to prove all the grounds for rejecting the claims. All of the elected claims, including those with current amendments, are now allowable in their current form. An early and favorable action is respectfully solicited.

If the Examiner wishes to discuss additional claim amendments to place the application in better form for allowance or any other issues related to this application, the undersigned attorney may be reached at the phone numbers, and mailing address herein below.

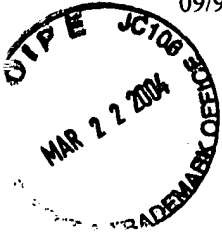
Applicants believe that no fee is due. However, the Commissioner is hereby authorized to charge any additional fees or credit any overpayments to Deposit Account No. 50-2980 maintained by The SUN Law Office PLLC.

Respectfully submitted,



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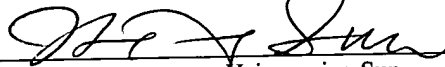
March 22, 2004

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